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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR		ATTORNEY DOCKET NO.
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EXAMINER	
GOLDBERG, J	
ART UNIT	**PAPER NUMBER**
1655	2

DATE MAILED: 09/22/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No.	Applicant(s)	
	09/613,887	HOGAN, KIRK	
	Examiner	Art Unit	
	Jeanine A Enewold Goldberg	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a)☐ All b)☐ Some * c)☐ None of the CERTIFIED copies of the priority documents have been:

1.☐ received.

2.☐ received in Application No. (Series Code / Serial Number) _____ .

3.☐ received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

15)☒ Notice of References Cited (PTO-892)
16)☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17)☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
18)☐ Interview Summary (PTO-413) Paper No(s). _____ .
19)☐ Notice of Informal Patent Application (PTO-152)
20)☐ Other:

DETAILED ACTION

Specification

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

It is noted that long lists of hyperlinks are provided on page 26 and 27, for example.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The essential elements of the claims are drawn to a method for selecting an operative course of action by detecting two or more genetic markers.

The specification teaches only a hand-full of mutations within ten different genes which have been identified as having any effect on the response to anesthesia. The specification provides four tables which illustrate the mutations in the specified genes and the percent of incidences.

There is not adequate description of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication. The specification only discloses ten genes associated with poor response to anesthesia. Further, within these ten genes only twenty specific mutations within the scope of the genus: genetic markers which may be used to screen for a patient's response to anesthesia and related medication. The general knowledge in the art concerning genetic markers which may be used to screen for a patient's response to anesthesia and related medication does not provide any indication of how to readily identify these genetic markers. The twenty mutations described are not representative of the genus of genetic markers which may be used to screen for a patient's response to anesthesia and related medication. There is substantial variability among the species of nucleic acids encompassed in the scope of the claim because only twenty specific mutations have been identified. The specification has also not defined a structural feature of the genetic markers which may be used to screen for a patient's response to anesthesia and related medication which would be common to all members of the genus that constitutes a substantial portion of the genus. Furthermore, one of skill in the art would conclude that applicant was not in possession of the claimed "genetic markers which may be used to screen for a patient's response to anesthesia and related medication" because the description of only twenty members of this genus is not representative of the variants of the genus and is insufficient to support the claims. Thus, the specification does not adequately provide a written description for genetic markers

which may be used to screen for a patient's response to anesthesia and related medication.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> **The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.**

3. Claims 1-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia based upon the detection of two or more genetic markers for use in generating a genomic profile which is used in selecting an operative course of action, does not reasonably provide enablement for detecting **any** two genetic markers and generating a profile for use in selecting **any** operative course of action. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are broadly drawn to providing a sample from a perioperative subject and detecting two or more genetic markers to generate a genomic profile for use in selecting an operative course of action.

The specification teaches ten distinct genes (namely, BCE, CYP2D6, MTHFR, MS, CBS, F 5 Leiden, Prothrombin, RYR1, CACNA1S and CPT 2) which contain 20 different mutations, as set forth in Tables 1-4, which may be used to detect possible

response to anesthesia. The specification teaches mutations in the ten identified genes as being associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia (pg. 48-49). The specification provides an extensive list of hyperlinks which provide sequence data for numerous markers (pg. 26-27).

The art teaches malignant hyperthermia (MH) is a pharmacogenetic disease with autosomal dominant inheritance triggered by exposure to commonly used inhalational anesthetics (Sudbrak et al. Human Mol. Genetics, Vol. 2, No. 7, pg. 857-862, 1993). Sudbrak excludes several loci which do not give support for a MH susceptibly locus. O'Brien et al (J. Med. Genet. Vol. 32, No. 11, pg. 913-914, 1995) teaches that Arg163Cys substitution in the RYR1 gene does not cosegregate with MH susceptibility (abstract). Moreover, O'Brien teaches that DHPR is unlikely to be a major cause of MH. Tsai et al (Am. J. Hum. Genet. Vol. 59, pg. 1262-1267, 1996) teaches that an insertion in the CBS gene seems to affect the activity of the CBS enzymes, the prevalence is somewhat increase in patients with premature coronary-artery disease, although not statistically significant. Hecht et al (Anesth. Analg, Vol. 84, pg. 461-464, 1997) teaches a G1583A mutation in CACNL1A3 which is associated with HypoPP. Hecht also teaches that HypoPP has been identified as a disorder that can predispose a patient to the syndrome of MH which the risk of triggering skeletal muscle contraction and rhabdomyolysis, together with earlier reports of flaccid paralysis aggravated by surgery and general anesthesia, appear to favor regional anesthesia in this population whenever feasible (abstract). Hecht also teaches that MH susceptibility associated with

HypoPP and of hypokalemia elicited by regional anesthesia suggests that hybrid anesthetic techniques be avoided (pg. 462, col. 2). Sachse et al (Am. J. Hum. Genet. Vol. 60, pg. 284-295, 1997) teaches that therapeutic efficacy and adverse events in treatment with many drugs depend on CYP2D6 activity, genotyping CYP2D6 may become a routine part of an individually optimized drug treatment (p 284, col. 2). Korte et al (Clin. Chem. Lab. Med, Vol. 36, No. 4, pg. 235-240, 1998) teaches to establish a possible "perioperative reference range" for thrombin generation prothrombin fragment F1+2 and fibrin degradation markers were measured (abstract). Korte also teaches that preoperative determination of molecular markers would be helpful in identifying a group of patients at high risk for intraoperative disorder of hemostasis by exclusion of low risk patients (abstract). As seen in Table 2 and Table 3, the results of the detection assay for the two genetic markers were observed (pg. 237).

Hogan (Current Opinion in Neurology, Vol. 11, pg. 469-476, 1998) teaches several mutant alleles at loci on chromosome 1q, 3q, 5p, 7q and 19q which account for up to 50% of MH susceptibility (abstract). Hogan proposes preoperative genotyping for panels of MHS alleles would benefit by selection of an alternate anesthetic (pg. 474, col. 1). Hogan extensively discusses the unpredictability in the RYR1 gene mutations and the relation to MH. Hogan teaches up to 17 mutations in the RYR1 gene have been identified (pg 471, col 1). "Most putative MH mutations are orphans appearing in single families, frequently in association with central core disease. Mutation analysis is rarely commensurate with IVCT results in full" (pg 471, col 1). Hogan further states that "when an identical mutation has arisen in more than an isolated pedigree, the correlation

varies from family to family" (pg 471 col 1). Further, Hogan teaches that "whether these observations are best explained by inaccurate diagnosis on the basis of the IVCT, lack of a causal relation between candidate polymorphisms and the malignant hyperthermia phenotype, or the possibility of two or more malignant hyperthermia-associated muations acting alone or in concert but segregating within a single pedigree, has not been ansered" (pg 471, col 2). Hogan explicitly states that "until very nearly all muations in all predisposing genes are charted, the causality for each is unambiguous, offering family genotyping for purposes other than research will be premature" (pg 474, col 1). Hogan teaches that "patients lacking the mutant alleles sought may not be clear of risk (pg 473, col 2).

Brandt et al (Hum. Mol. Genetics, Vol 8, No. 11, pg 2055-2062, 1999) teaches screening of approximately 105 MH families for mutations. Despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2). De Stefano et al (New England J. Med, Vol 341, pg 801-806, 1999) teaches screening for two point mutations, one in F 5 Leiden and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation.

Based upon the teachings in the specification and the art, the skilled artisan would be unable to practice the invention as broadly as claimed. First, the specification only provides twenty mutations which have association with "selection an operative course of action". It would be undue experimentation for the skilled artisan to study the voluminous known mutations and determine association with anesthesia and medical complications. Limiting the scope of the claims to recite the ten genes would still require undue experimentation for the skilled artisan to evaluate the large number of known mutations in these genes and determine the association with anesthesia complications.

Secondly, the specification only contemplates butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia (pg. 48-49). The specification does not provide genetic markers for use in selecting **any** operative course of action. The specification does not teach any specific combination of markers and what the appropriate "operative course of action" entails. It would require undue experimentation for the skilled artisan to minimally take the 20 mutations provided in the specification and determine appropriate courses of action for all of the various combinations if detected. Such combinations would include all of the different pairs of mutations, all of the different triples of mutations and so forth. The skilled artisan would be required to identify subjects which had all of the combinations and determine what the "operative course of action" would be for any scenario which is unreasonable. Furthermore, the specification does not provide any guidance as to how to select the specific anesthesia based solely upon these markers and their correlation to an invasive

versus non-invasive procedure. The specification provides no distinction between genetic markers which are useful in general anesthesia versus region anesthesia. It is unclear whether these markers have the same effect in determining complications for each type of anesthesia or whether different markers has different effects. The specification does not appear to provide any distinction between different types of anesthesia and their association with different mutations. It is unpredictable for the skilled artisan to determine which of the provided mutations would have complications with specific anethestics. The specification does not teach how different types of surgery are associated with the genetic markers, i.e. non-invasive and invasive surgery. It is unclear how the skilled artisan would differentiate the information obtained from the genomic profile for obtaining information for non-invasive and invasive surgery since the specification does not provide any differentiation. While the claim is not particularly limited to these 20 mutations, the skilled artisan would be unable to practice the invention limited to this scope without undue experimentation.

Thirdly, based upon the teachings in the art, the detection of two genetic markers would not necessarily provide enough information to select an operative course of action appropriate for a particular patient. The art teaches "most putative MH mutations are orphans appearing in single families, frequently in association with central core disease. Mutation analysis is rarely commensurate with IVCT results in full" (Hogan, pg 471, col 1). Hogan further states that "when an identical mutation has arisen in more than an isolated pedigree, the correlation varies from family to family" (pg 471 col 1). Hogan explicitly states that "until very nearly all mutations in all predisposing genes are

charted, the causality for each is unambiguous, offering family genotyping for purposes other than research will be premature" (pg 474, col 1). Brandt teaches despite the extensive number of known mutations in RYR1, "interpretation must be performed with care because lack of the particular mutation segregating in the family does not exclude absence of further independent unknown mutations. Additionally, genetic screening is not yet suitable for routine diagnostics due to the low incidence of each mutation and the vastness of the gene" (pg 2058, col 2). Thus, the skilled artisan would expect unpredictability in assaying for two genetic markers and subsequently determining an appropriate course of action. It would unpredictable for the skilled artisan as taught by Hogan and Brandt.

Therefore, it would be undue experimentation for the skilled artisan to detect **any** genetic markers and infer an association between the makers and response to anesthesia based solely upon the guidance provided in the specification which teaches twenty mutations which are associated with Butyrylcholinesterase deficiency, poor debrisiquine metabolism, thrombus, and malignant hyperthermia, respectively (pg. 48-49).

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 1-20 are indefinite because the claims do not recite a positive process step which clearly relates back to the preamble. The claims 1, 13 and 17 lack a preamble which sets out the intent of the claims. Thus, the preamble does not meet the final process step.

B) Claims 1-20 are indefinite over the recitation providing "an assay" because it is unclear how an assay may be provided. One may clearly imagine the reagents necessary for a set assay be provided, but for one to provide an assay is unclear.

C) Claims 1-20 are indefinite over the recitation "for use in selecting an operative course of action" because it is unclear whether generating a genomic profile meets the limitations of the claims or whether the claim limitations require the genomic profile is in fact used for selecting an operative course of action. Furthermore, it is unclear what an operative course of action includes. It is unclear whether an operative course of action may essentially be any course of action which is operative, i.e. which works.

D) Claims 1-20 are indefinite over the recitation "two or more genetic markers" because it is unclear whether detection of a gene constitutes a genetic marker, detection of a chromosome is genetic marker, absence of detecting a chromosomal region is a genetic marker or whether a mutation within a gene which varies between individuals must be detected.

E) Claim 2-6 are indefinite because it is unclear whether the course of action taken following generating a genomic profile may include abstaining from administering anesthesia, or whether the course of action will include administering anesthesia, however may include additional drug administration.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> **A person shall be entitled to a patent unless –**
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

2. Claims 1, 13 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Vogelstein (US Pat. 5,380,645, January 1995).

Vogelstein teaches a method for assessment of colorectal cancer by detecting genetic changes. Specifically, Vogelstein teaches a study in which allelic loss in patients was determined. For example, as seen in Table II, the first patient, as indicated by S7, was identified to have chromosomal arms on which allelic markers were lost for three distinct chromosomal arms. Thus, this perioperative subject, was subjected to an assay which identified two or more genetic markers, i.e. 7q, 18q and 20p, in which a

genetic profile was generated. This patient was thus grouped in Group II of the Vogelstein study which suggested that the patients were more likely to die with or from their cancer (col. 13, lines 1-5). Vogelstein also states "the measurement of allelic losses might help to identify patients with an otherwise relatively favorable prognosis who could benefit from additional therapy" (col. 13, lines 29-31).

3. Claims 1, 8-10, 13-14 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by Sachse (Am. J. Hum. Genet. Vol. 60, pg. 284-295, 1997).

Sachse teaches a method which samples individuals which are prior to any operative procedure and detecting two or more genetic markers such that a genomic profile is established and an 'operative course of action' is determined. Sachse teaches performing PCR reactions 1-4 of table 1 routinely to detect the most frequent PM alleles and a test for the CYP2D6 gene duplication. Sachse teaches that therapeutic efficacy and adverse events in treatment with many drugs depend on CYP2D6 activity, genotyping CYP2D6 may become a routine part of an individually optimized drug treatment (p 284, col. 2).

4. Claims 1, 8-17, 20 are rejected under 35 U.S.C. 102(b) as being anticipated by De Stefano et al (New England J. Med, Vol 341, pg 801-806, September 1999)

De Stefano et al teaches screening for two point mutations, one in F 5 Leiden and one in the prothrombin gene which are the most common causes of inherited thrombophilia. Thus, carriers of both of these mutations have an increased risk of

recurrent deep venous thrombosis after a first episode and are candidates for lifelong anticoagulation. The two mutations studied were F 5 Leiden and G20210A prothrombin mutation. Both of these mutations are thought to be separately associated with thrombosis.

Conclusion

5. No claims allowable.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Enewold Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Thursday from 7:00AM to 4:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Jeanine Enewold Goldberg
September 14, 2000

LISA B. ARTHUR
PRIMARY EXAMINER
GROUP ~~1800~~ 1600